



# Annual Surveillance Summary: *Pseudomonas aeruginosa* Infections in the Military Health System (MHS), 2015

NMCPHC-EDC-TR-195-2017

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## Abstract

*Pseudomonas aeruginosa* is an opportunistic gram-negative bacterium that can cause severe illness in the immunocompromised. Its minimal nutritional requirements allow it to survive and thrive in both community and hospital settings. In 2015, the incidence rate of *P. aeruginosa* was 32.6 per 100,000 persons per year in the Military Health System (MHS). This rate reflects a 13.6% increase from the weighted historic baseline from the preceding three years. The South and West regions had the highest incidence rates (43.0 per 100,000 persons per year and 39.9 per 100,000 persons per year, respectively), but the South and South Atlantic regions had the highest incidence of multidrug-resistant (MDR) infections (3.8 per 100,000 persons per year and 2.2 per 100,000 persons per year, respectively). Among all MHS beneficiaries, 47.0% of *P. aeruginosa* infections were healthcare-associated (HA) cases. *P. aeruginosa* infections were most susceptible to colistin, piperacillin, and doripenem with average susceptibility to all around 95.0%. *P. aeruginosa* infections did not display 100.0% susceptibility to any tested antibiotic in the MHS in 2015. Continued surveillance of *P. aeruginosa* is recommended.



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## Background

Pseudomonads are gram-negative, aerobic, rod-shaped bacteria that are found in soil, decaying organism matter, vegetation, and water.<sup>1</sup> The most clinically significant of more than 140 *Pseudomonas* species is *Pseudomonas aeruginosa*. It has minimal nutritional requirements and a tolerance to a wide range of physical conditions.<sup>2</sup> These traits have allowed *P. aeruginosa* to survive over time and to persist in both community and hospital settings.<sup>3</sup>

In the 1940s, distinguishable microbiologic characteristics separating *P. aeruginosa* from other *Pseudomonas* species were identified.<sup>4</sup> *P. aeruginosa* first garnered wide interest when it was associated with burn infections and war-related wounds. During the 1950s and 1960s, attention grew as the incidence of *P. aeruginosa* in burn patients increased and effective antibiotic options decreased. *P. aeruginosa* was one of the three most common wound pathogens during the Vietnam War, and in the 1980s it represented the single most frequently isolated pathogen in patients with nosocomial pneumonia, as well as burn-wound infections.<sup>5,6</sup> By the late 1990s, *P. aeruginosa* became recognized as a prevalent opportunistic human pathogen and one of the most common gram-negative bacterium found in nosocomial infections.<sup>7</sup>

*P. aeruginosa* has a well-documented clinical history as associated with burn and wound infections; however, recent manifestations of *P. aeruginosa* include pneumonias in cystic fibrosis patients, endocarditis in drug addicts, postoperative wound infections, urinary tract infections (UTIs), and sepsis.<sup>5</sup> A true community-acquired *P. aeruginosa* infection among patients without any prior health care exposure is rare, as *P. aeruginosa* is not part of a healthy human's microbiota.<sup>2</sup> Colonization typically occurs after a patient's hospitalization and antimicrobial exposure.<sup>5</sup> Water is one of the most common exposures linked to a *P. aeruginosa* outbreak. Common community-acquired infections include ulcerative keratitis, otitis externa, and skin and soft tissue infections (SSTIs).<sup>8</sup> Community-acquired infections are commonly linked to recreational water use, contact lens use, home humidifiers, soil, and vegetables.<sup>3,8,9</sup>

According to data reported to the National Healthcare Safety Network (NHSN) at the Centers for Disease Control and Prevention (CDC), *P. aeruginosa* is the fifth most common pathogen implicated in all hospital-acquired infections.<sup>10</sup> *P. aeruginosa* is the most common gram-negative bacteria implicated in nosocomial pneumonia and the second most common pathogen implicated in ventilator-associated pneumonia.<sup>5</sup> Common hospital-acquired infections include pneumonias, UTIs, blood stream infections (BSIs), surgical site infections, and skin infections.<sup>8</sup> Hospital-acquired infections are estimated to complicate 5 to 10% of hospitalizations in the United States (US) annually, leading to increased health care costs and prolonged hospitalizations.<sup>11</sup> The CDC estimates that there are about 51,000 healthcare-associated *P. aeruginosa* infections in the US per year.<sup>12</sup> When a microbiological agent is identifiable, 11.3 to 13.8% of all nosocomial infections are caused by *P. aeruginosa*. This percentage increases in infections reported in intensive care units (ICUs) by 13.2 to 22.6%.<sup>8</sup>

*P. aeruginosa* is now regarded as a “superbug.” It is often resistant to multiple antibiotics and continues to develop resistance to others. *P. aeruginosa* is intrinsically resistant to a broad selection of antibiotic classes including many  $\beta$ -lactams, tetracyclines, aminoglycosides, and



fluoroquinolones, but it also has the ability to develop acquired and adaptive resistance, making it difficult to eradicate.<sup>8,13</sup> The intrinsic resistance of *P. aeruginosa* is due to the low permeability of its outer membrane. This feature is genetic and allows the secondary and adaptive resistance mechanisms to work more efficiently.

Typically, infections that are categorized as multidrug-resistant (MDR) will exhibit several resistance mechanisms simultaneously.<sup>8</sup> Overuse of broad spectrum antibiotics has led to a rapid increase in MDR *P. aeruginosa*.<sup>14</sup> *P. aeruginosa* has the ability to develop resistance to an antibiotic during the course of treating the infection.<sup>3</sup> According to the CDC, in 2013 there were 6,700 MDR infections of *P. aeruginosa* that resulted in 440 deaths.<sup>12</sup> Infections caused by resistant strains have been found to be associated with a three-fold higher rate of mortality, a nine-fold higher rate of secondary bacteremia, a two-fold increase in the length of hospital stay, and a noticeable increase in healthcare costs.<sup>15</sup>

It is important, therefore, to monitor *P. aeruginosa* trends and changes in epidemiology on an ongoing basis. This analysis presents surveillance of *P. aeruginosa* infection burden among Military Health System (MHS) beneficiaries in calendar year (CY) 2015. This report describes the demographics, clinical characteristics, prescription practices, and antibiotic susceptibility patterns for *P. aeruginosa* infections among MHS beneficiaries and Department of the Navy (DON) active duty service members with deployment-related infections.





## Methods

The EpiData Center (EDC) at the Navy and Marine Corps Public Health Center (NMCPHC) conducted retrospective surveillance of *P. aeruginosa* infection in the MHS in CY 2015 (01 January 2015 to 31 December 2015). Health Level 7 (HL7)-formatted Composite Health Care System (CHCS) microbiology data was used to identify positive *P. aeruginosa* laboratory results. A unique *P. aeruginosa* infection was defined as the first positive *P. aeruginosa* laboratory result per person per 30 days. Incidence represented the first unique infection per person per calendar year and prevalence was defined as all unique *P. aeruginosa* infections.

## Demographic Classification

Demographic information for each incident infection was described using data within the HL7-formatted CHCS microbiology record and infections were classified according to the patient's gender, age, sponsor service (Air Force, Army, Marine Corps, or Navy), duty status (Active Duty, Retired, Family Member, or Other), and region of the facility where the specimen was collected. The Active Duty category included both active duty and recruit personnel, defined by the beneficiary type codes of 11 and 13, respectively.

*P. aeruginosa* incidence rates and prevalence infections were aggregated into six spatial regions and visualized as maps created in ESRI ArcGIS software (version 10.2.2). Organisms identified in each region may act as a reservoir within that region and contribute to the burden of exposure. Geographic regions were assessed within the continental United States (CONUS) and outside the CONUS (OCONUS), with the spatial regions identified as follows:

- **Northeast:** Maine, New Hampshire, Vermont, Massachusetts, Rhode Island, Connecticut, New York, Pennsylvania, New Jersey.
- **Midwest:** Michigan, Wisconsin, Minnesota, Ohio, Indiana, Illinois, Iowa, Missouri, Kansas, Nebraska, North Dakota, South Dakota.
- **West:** California, Oregon, Washington, Idaho, Montana, Wyoming, Colorado, New Mexico, Arizona, Utah, Nevada, Alaska, Hawaii.
- **South:** Texas, Oklahoma, Arkansas, Louisiana, Mississippi, Alabama, Tennessee, Kentucky.
- **South Atlantic:** Delaware, Maryland, District of Columbia, Virginia, West Virginia, North Carolina, South Carolina, Georgia, Florida.
- **OCONUS:** All US territories and non- US countries.<sup>16</sup>

## Clinical Characteristics Classification

Clinical characteristics were described for prevalent infections using information within the HL7-formatted CHCS microbiology record. Specimens were classified as inpatient or outpatient based on the Medical Expense and Performance Reporting System (MEPRS) codes of the location where the specimen was collected. A MEPRS code of A indicated specimen collection in the inpatient setting. All other MEPRS codes were considered outpatient encounters.



Infections were classified into invasive and non-invasive categories using the specimen source or body site variables in the HL7-formatted CHCS microbiology record. The terms used to group the data into these categories are described in Table 1. In addition, infections were further categorized based on body collection sites specific to the organism of interest (e.g., urine, respiratory, bloodstream) to provide enhanced granularity to the source of infection. Clinical characteristics were presented as a proportion of all infections within the population meeting the definition criteria.

**Table 1.** Invasive and Non-Invasive Infection Classification for *P. aeruginosa* Infections Accessing the MHS

Infection Classification	If Body Site or Specimen Source Sample Taken From:
Invasive Infections	Blood, bone, cerebrospinal fluid, peritoneal fluid, pleural fluid, or synovial fluid
Other Non-Invasive Infections	Abscess, aspirate, body fluid, boil, bursa, carbuncle, cellulitis, cyst, discharge, drainage, exudate, eye, genital, lesion, pus, pustule, respiratory, skin, sputum, stool, swab, throat, tissue, urine, or wound

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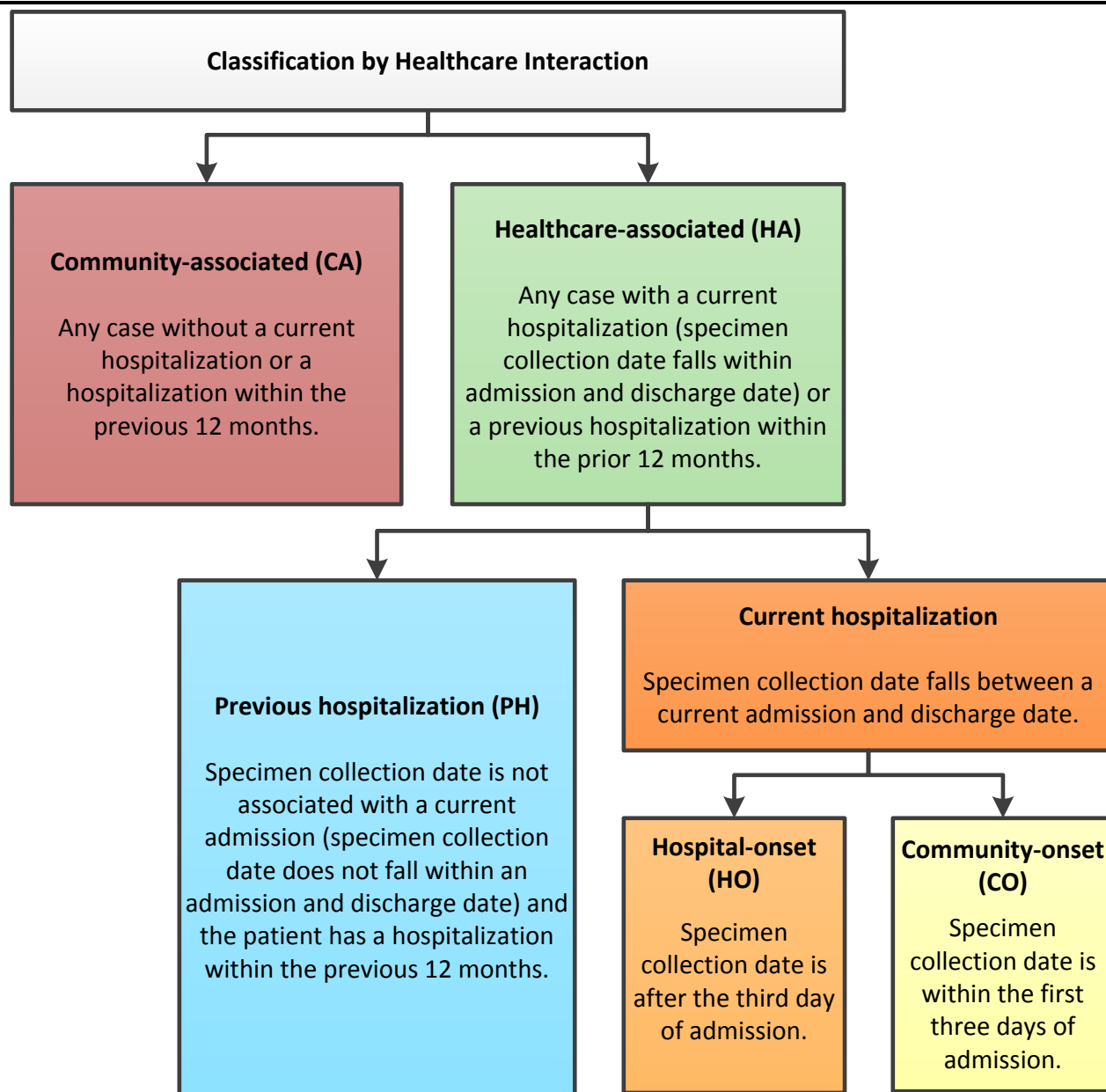
### Epidemiologic Infection Classification

To evaluate all laboratory-confirmed *P. aeruginosa* infections for recent contact with the healthcare system, *P. aeruginosa* prevalence infections were matched to the Standard Inpatient Data Record (SIDR) to determine epidemiologic infection classification. Records were categorized as either community-associated (CA) or healthcare-associated (HA). CA cases were defined as patients without a current hospitalization nor a hospitalization in the previous 12 months. HA cases were defined as patients who were hospitalized at the time of infection (currently hospitalized) or who had a hospitalization within the previous 12 months. Current hospitalizations were further categorized as a hospital-onset (HO) case or a community-onset (CO) case. HO cases were defined as patients with *P. aeruginosa* identified after the third day of the current admission. CO cases were identified as patients with a specimen collected within the first three days of the current admission yielding *P. aeruginosa*, indicating the patient likely acquired the organism within the community.<sup>17</sup> Figure 1 presents the definitions for epidemiologic infection classifications.





**Figure 1. Epidemiologic Infection Classifications<sup>a</sup>**



<sup>a</sup>Cohen A, Calfee D, Fridkin SK, et al. Recommendations for metrics for multidrug-resistant organisms in healthcare settings: SHEA/HICPAC position paper. *Infect Cont Hosp Ep*. 2008;29(10):901-913. Prepared by the EpiData Center Department, Navy and Marine Corps Public Health Center, on 28 February 2017.

### Exposure Burden Metrics

Only the first unique multidrug-resistant organism (MDRO) infection per patient per admission was used to analyze exposure burden metrics in the MHS. Admission prevalence estimated the



exposure of infection at the time of admission (importation of MDROs into the MHS), which included MDROs isolated from samples collected up to and including the third day of admission, as well as samples that tested positive for infection in the prior calendar year. Overall prevalence included all individuals with an MDRO infection identified from a sample collected at any point during the admission, or samples that tested positive for infection in the prior calendar year. Admitted patients with a history of colonization or infection were identified by searching prevalence infection MDROs from the prior calendar year to determine a history of infection. These beneficiaries were counted in both the admission and overall prevalence populations as they contributed to the colonization pressure and exposure burden for those not already colonized or infected in both populations.<sup>17</sup> The historical review of data is included to show a reservoir of antimicrobial resistance and pressure among *P. aeruginosa* infections. Regional rates of exposure burden were calculated as the rate of exposure (admission or overall prevalence) per 1,000 inpatient admissions per region per year.

### Pharmacy Transactions

To analyze antimicrobial prescription practices in the MHS, the HL7-formatted microbiology *P. aeruginosa* prevalence infections were matched to pharmacy data to identify antibiotic prescriptions associated with *P. aeruginosa* infections in all pharmacy databases (outpatient oral (OP), inpatient oral (unit dose, or UD), and inpatient and outpatient intravenous (IV)). Prescriptions were considered to be associated with a *P. aeruginosa* infection if the transaction date in the pharmacy record occurred either seven days before or after the date the specimen was certified in the laboratory data. All pharmacy transactions, regardless of database source (UD, IV, OP), were evaluated as one data source. Cancelled prescriptions or those with zero or null filled prescriptions were removed prior to analysis. A unique antibiotic prescription was defined as the first dispensed prescription for an antibiotic per prevalence infection. Antimicrobials recommended for treatment of *P. aeruginosa* infections according to the Johns Hopkins Antibiotic Guide were retained for analysis.<sup>18</sup>

### Antimicrobial Resistance Classification

To evaluate changes in antimicrobial susceptibility for *P. aeruginosa* infections, an antibiogram was created using antibiotic susceptibility results from the microbiology record according to the Clinical and Laboratory Standards Institute (CLSI) guidelines.<sup>19</sup> The antibiogram includes the first isolate per person per organism per year from 2010 to 2015. The Cochran-Armitage trend test was used to assess patterns in susceptibility across years. Trend direction for a single antibiotic over time was established using the two-tailed *P*-value; an increase in susceptibility was denoted by a green upward arrow and a decrease in susceptibility was denoted by a blue downward arrow. A statistically significant trend was established using a *P*-value  $\leq .05$ .

Susceptibility results from the microbiology record were used to establish the level of antibiotic resistance among prevalent infections. Specimens that were non-susceptible (resistant or intermediately susceptible) to at least one antibiotic from at least three different antibiotic classes were considered MDR. The antibiotic classes of interest in this classification included aminoglycosides, antipseudomonal carbapenems, antipseudomonal cephalosporins, antipseudomonal fluoroquinolones, antipseudomonal penicillins +  $\beta$ -lactamase inhibitors,



monobactams, phosphonic acids, and polymyxins. Possible extensively drug-resistant (PXDR) infections were those organisms non-susceptible to some or all antimicrobials tested in an antimicrobial category but not tested against all antimicrobial categories in the definition and could therefore not be included or excluded as an XDR infection. Organisms that were non-susceptible to at least one antibiotic in all but two classes of eight total classes in the definition were considered extensively drug-resistant (XDR). Possible pandrug-resistant (PPDR) infections were those that could not be definitively identified as XDR based on the XDR definition and were non-susceptible to all antibiotics tested but were not tested against all antibiotics in the definition and could therefore not be excluded as a PDR infection. Finally, pandrug-resistant (PDR) organisms were organisms that were non-susceptible to all antibiotics in all antibiotic classes in the definition.<sup>20</sup> For the remainder of this report, unless otherwise stated, resistant and resistance are defined as *P. aeruginosa* infections having any level of antibiotic resistance, whether it be MDR, PXDR, XDR, PPDR, or PDR. See Appendix A (Table A1) for a list of antibiotics used to identify the level of resistance among infections.

## Special Populations

*P. aeruginosa* infections identified among DON active duty personnel were matched to the Defense Manpower Data Center (DMDC) Contingency Tracking System (CTS) to explore deployment-related infections occurring on or between the start and end dates of the deployment plus 30 days. Thirty days post-end of deployment was used to ensure all *P. aeruginosa* infections related to the deployment were included. Records with no deployment end date (i.e., service member remains deployed) were also included provided that the infection occurred in the analysis year (2015) and the start date of deployment was within 180 days of the specimen certification date.

## Statistical Analysis

The MHS Data Mart (M2) was used to obtain counts of TRICARE eligible MHS beneficiaries for denominators. The annual incidence rate was defined as the count of all incident infections per year divided by the corresponding annual M2 eligible beneficiary count (represented by the count in July) per year. A weighted average of incidence rates by month for the three years prior to the current analysis year (weighted historic monthly baseline) was used to assess the seasonal component of *P. aeruginosa* infections in 2015. One and two standard deviations, both above and below the weighted historic monthly baseline, were used to indicate statistically significant changes in incidence rates of *P. aeruginosa* infections in the analysis year.

All incidence rates are presented as an estimated rate per 100,000 persons per year. Due to the transient nature of the military beneficiary population and an inability to account for the proportion of the beneficiary population that receives medical care outside of the MHS, estimated rates are used for comparison of rates from year to year. A historical baseline was created using the weighted average of the immediately preceding three years. The historical baseline of the incidence rate serves as a clinical reference for the 2015 incidence rate. Two standard deviations on either side of the baseline were calculated to assess variation in incidence rate in the three years prior to the current evaluation period. Two standard deviations provide the



upper and lower bounds (approximately 95%) for assessing whether the observed occurrence was likely due to chance, and for consideration of clinically significant trends.



## Results

### Section A – Descriptive Epidemiology

#### Incidence of *P. aeruginosa*

The annual incidence rate (IR) for *P. aeruginosa* infection among all MHS beneficiaries in 2015 was 32.6 per 100,000 persons per year (Table 2). This rate is 13.6% above the weighted historic IR from 2012 to 2014, but within two standard deviations. Across all service populations in the MHS, the IR was between 8-17% above the service weighted historic rate. The highest incidence rate was seen in the Marine Corps beneficiary population with a rate of 34.2 infections per 100,000 persons per year, 13.9% above the historical baseline. The greatest percent change was observed in the Army beneficiary population, which was the only service population with an IR for 2015 outside of two standard deviations.

**Table 2.** Incidence Rate (IR) for *P. aeruginosa* Infections in the MHS, CY 2015

Population	2015 IR	Weighted Historic <sup>a</sup> IR 2012 - 2014	Two Standard Deviations: Weighted Historic <sup>a</sup> IR	2015	
				Direction	Percent Change <sup>b</sup>
MHS	32.6	28.7	5.2	↑	13.6%
Air Force	28.4	25.0	7.2	↑	13.6%
Army	29.9	25.7	3.0	↑	16.6%
Marine Corps	34.2	30.0	9.6	↑	13.9%
Navy	28.8	26.3	5.4	↑	9.5%
DOD Active Duty	29.2	27.0	4.4	↑	8.1%

Rates are presented as the rate per 100,000 persons per year.

A green arrow indicates an increasing percent change and a blue arrow indicates a decreasing percent change.

<sup>a</sup> Historic IR reflects the weighted average of the three years prior to the analysis year.

<sup>b</sup> This reflects the percent change from the weighted historic IR to the IR of the current analysis year. Data Source: NMCPHC HL7-formatted CHCS microbiology and MHS M2 databases.

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## Demographic Distribution of *P. aeruginosa*

Rates of *P. aeruginosa* were highest in beneficiaries that were male, aged 65 years and older, and retired (Table 3). Males had an incidence rate of 35.1 per 100,000 persons per year compared to a slightly lower rate of 30.0 per 100,000 persons per year among females. Individuals aged 65 years and older had an incidence rate of 50.1 per 100,000 persons per year. Although family members had the highest incident infection count, their incidence rate was the smallest by beneficiary type. Retired beneficiaries had an incidence rate of 33.9 per 100,000 persons per year, followed by active duty beneficiaries with an incident rate of 29.2 per 100,000 persons per year.

**Table 3.** Demographic Characteristics of *P. aeruginosa* Infections in the MHS, CY 2015

	N = 3,074	
	Count	Rate
<b>Gender</b>		
Female	1,392	30.0
Male	1,682	35.1
<b>Age Group (in Years)</b>		
0-17	570	29.0
18-24	257	22.2
25-34	329	27.4
35-44	196	23.5
45-64	626	30.0
65+	1,096	50.1
<b>Beneficiary Type</b>		
Active Duty	402	29.2
Family Members	1,535	27.8
Retired	736	33.9
Other <sup>a</sup>	401	--

<sup>a</sup> Rate is not reported due to variation in population denominator.

Rates are presented as the rate per 100,000 persons per year.

Data Source: NMCPHC HL7-formatted CHCS microbiology database.

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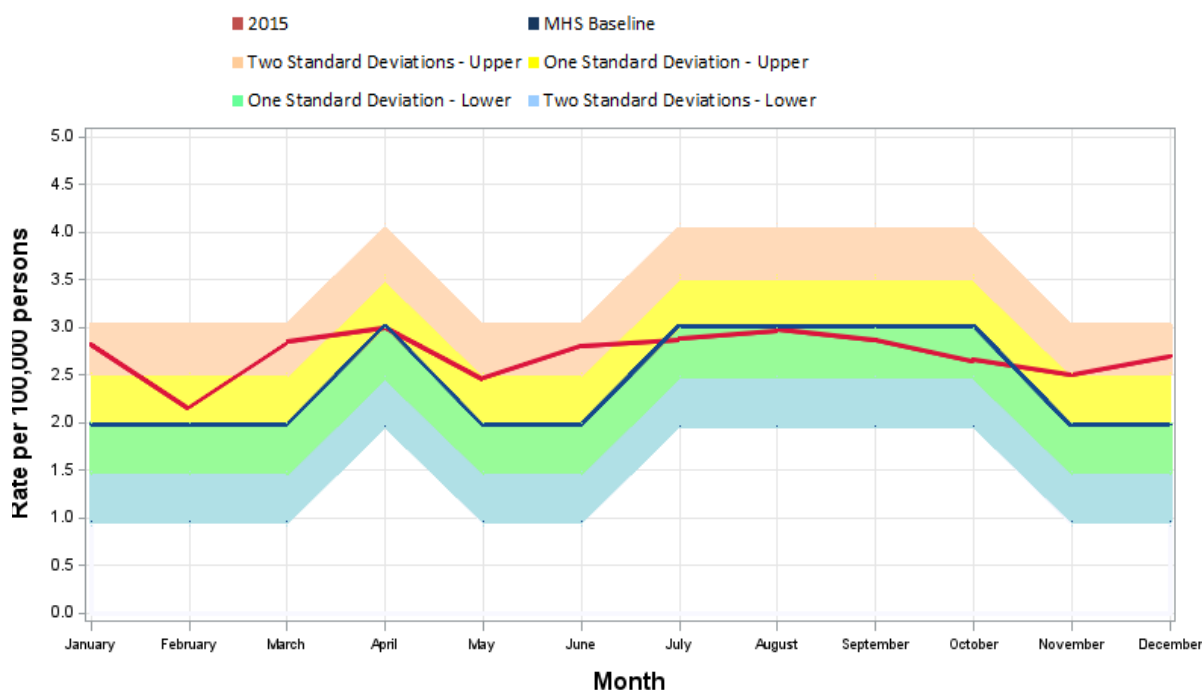




## Seasonality

Historically, *P. aeruginosa* incident infections have had a slight seasonal trend in the MHS, moderately increasing in the late summer. In 2015, however, the incidence rate by month remained stagnant and no month-to-month or seasonal change was evident (Figure 2). The incidence was highest with a rate of 3.0 per 100,000 persons per year in both April and August. The incidence rate was lowest in February, at 2.0 per 100,000 persons per year.

**Figure 2.** Monthly Incidence of *P. aeruginosa* Infections and Baseline Comparisons in the MHS, CY 2015



Rates are presented as the rate per 100,000 persons per year.

Bands indicate one and two standard deviations above and below the weighted historic monthly baseline.

The monthly baseline is a weighted average of the three years prior to the analysis year.

Data Source: NMCPHC HL7-formatted CHCS microbiology and MHS M2 databases.

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### *P. aeruginosa* Clinical Characteristics

The majority of unique *P. aeruginosa* infections were found in the outpatient setting (80.8%), were non-invasive (84.6%), and were collected from the urinary and respiratory tracts (37.0 and 29.0%, respectively). Only 1.8% of prevalent infections were collected from the bloodstream, and 19.2% of *P. aeruginosa* infections were collected in the inpatient setting (Table 4).

**Table 4.** Clinical Characteristics of *P. aeruginosa* Prevalence Infections in the MHS, CY 2015

	N = 3,587	
	Count	Percentage
<b>Specimen Collection Location</b>		
Inpatient	690	19.2
Outpatient	2,897	80.8
<b>Infection Type</b>		
Invasive	553	15.4
Other Non-Invasive	3,034	84.6
<b>Body Collection Site</b>		
Blood	64	1.8
Respiratory	1,040	29.0
SSTI/Wound	820	22.9
Urine	1,326	37.0
Other	337	9.4

Data Source: NMCPHC HL7-formatted CHCS microbiology database.

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## Exposure Burden Metrics

Table 5 presents two different metrics defining MDRO infection rates for healthcare-associated exposures. In 2015, there were 252,751 inpatient admissions across all MHS military treatment facilities (MTFs). The overall MDRO prevalence rate for *P. aeruginosa* was 0.9 per 1,000 inpatient admissions per year; this measures the exposure of infection at any point during the admission or one year prior. The admission MDRO prevalence rate for *P. aeruginosa* was 0.7 per 1,000 inpatient admissions per year; this measures the magnitude of infection at the time of admission (importation of the MDRO into the healthcare system) or one year prior. This implies that majority of the overall MDRO prevalence counts were collected within the first three days of admission, and were likely community-onset (CO) as opposed to hospital-onset (HO). Overall and admission MDRO prevalence rates were highest in the US South region (1.7 and 1.4 per 1,000 inpatient admissions per year, respectively) There were no MDRO admissions identified in the US Northeast region.

**Table 5.** MDRO Healthcare-Associated Exposure Burden Metrics among *P. aeruginosa* in the MHS, CY 2015

	Overall MDRO Prevalence <sup>a</sup>		Admission MDRO Prevalence <sup>b</sup>	
	Count	Rate <sup>c</sup>	Count	Rate <sup>c</sup>
<b>Region</b>				
OCONUS	2	--	2	--
US Midwest	3	--	2	--
US Northeast	0	--	0	--
US South	102	1.7	84	1.4
US South Atlantic	78	0.9	62	0.7
US West	43	0.5	32	0.4
<b>Total</b>	<b>228</b>	<b>0.9</b>	<b>182</b>	<b>0.7</b>

<sup>a</sup> Overall MDRO prevalence included all individuals with an MDRO infection identified from a sample collected at any point during the admission, as well as samples that tested positive for infection in the prior calendar year.

<sup>b</sup> Admission MDRO prevalence included all individuals with an MDRO infection identified from samples collected up to and including the third day of admission, as well as samples that tested positive for infection in the prior calendar year.

<sup>c</sup> Rates are presented as the rate per 1,000 inpatient admissions per year. Rates are not provided when the prevalence count is less than or equal to 5.

Data Source: NMCPHC HL7-formatted CHCS microbiology database.

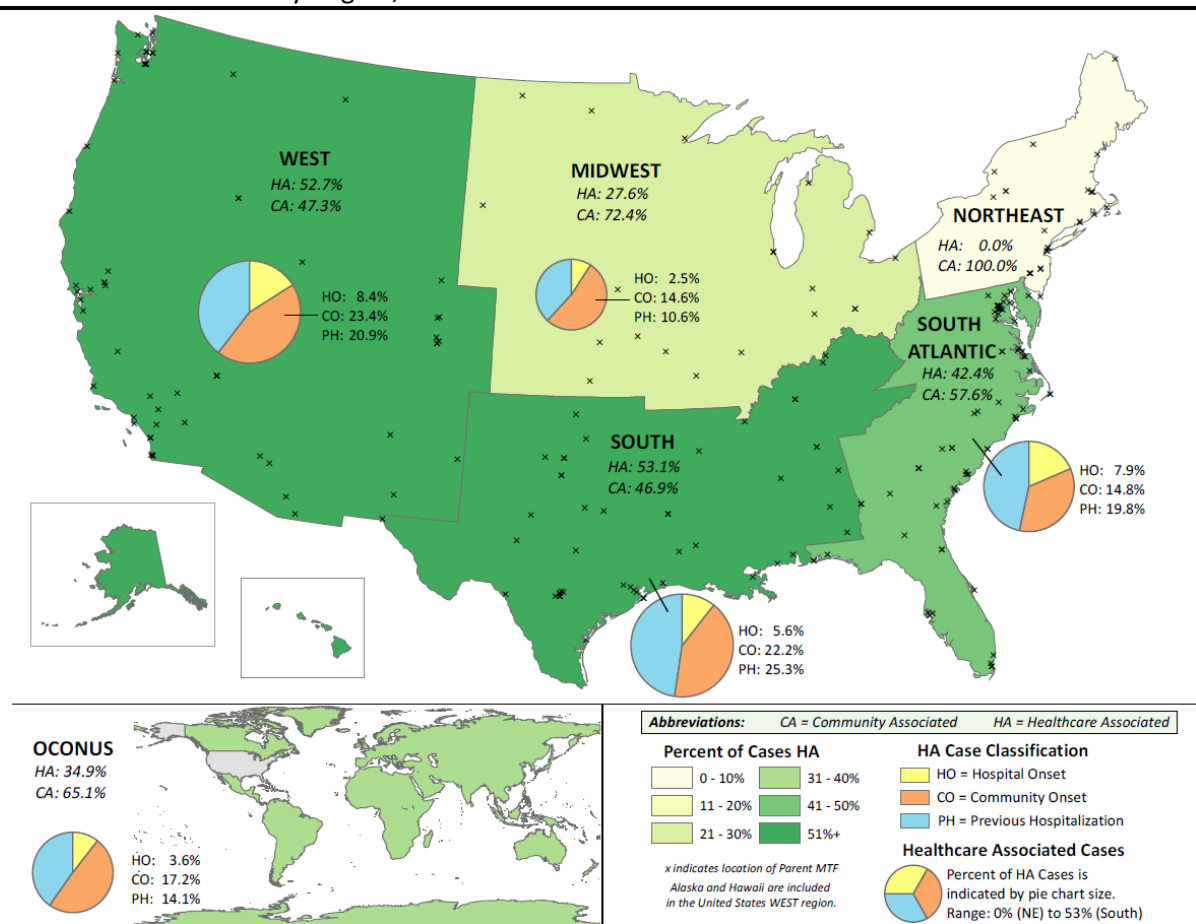
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## Regional Epidemiologic Infection Classifications

In 2015, 47.0% of unique *P. aeruginosa* infections were considered HA cases. Most of the HA cases were classified as CO or previous hospitalization (PH) cases, with only 6.9% overall classified as HO cases. Over 50.0% of unique *P. aeruginosa* infections in the West and South regions were classified as HA (Figure 3). In the West, the majority of HA *P. aeruginosa* cases were CO; in the South, the majority were PH cases. The West had the greatest proportion of HO *P. aeruginosa* infections at 8.4% of all unique *P. aeruginosa* infections. The proportion of HA cases in the South Atlantic was 42.4%, but the South Atlantic had the second highest proportion of HO *P. aeruginosa* infections at 7.9%. The Midwest had the smallest proportion of HO *P. aeruginosa* cases at 2.5%. The proportion of HA cases was smallest in the Midwest (27.6%) and in the Northeast, where there were no recorded HA cases.

**Figure 3.** Proportion of Healthcare and Community-Associated Cases among *P. aeruginosa* Infections in the MHS by Region, CY 2015



Data Source: NMCPHC HL7-formatted CHCS microbiology, SIDR, and MHS M2 databases.

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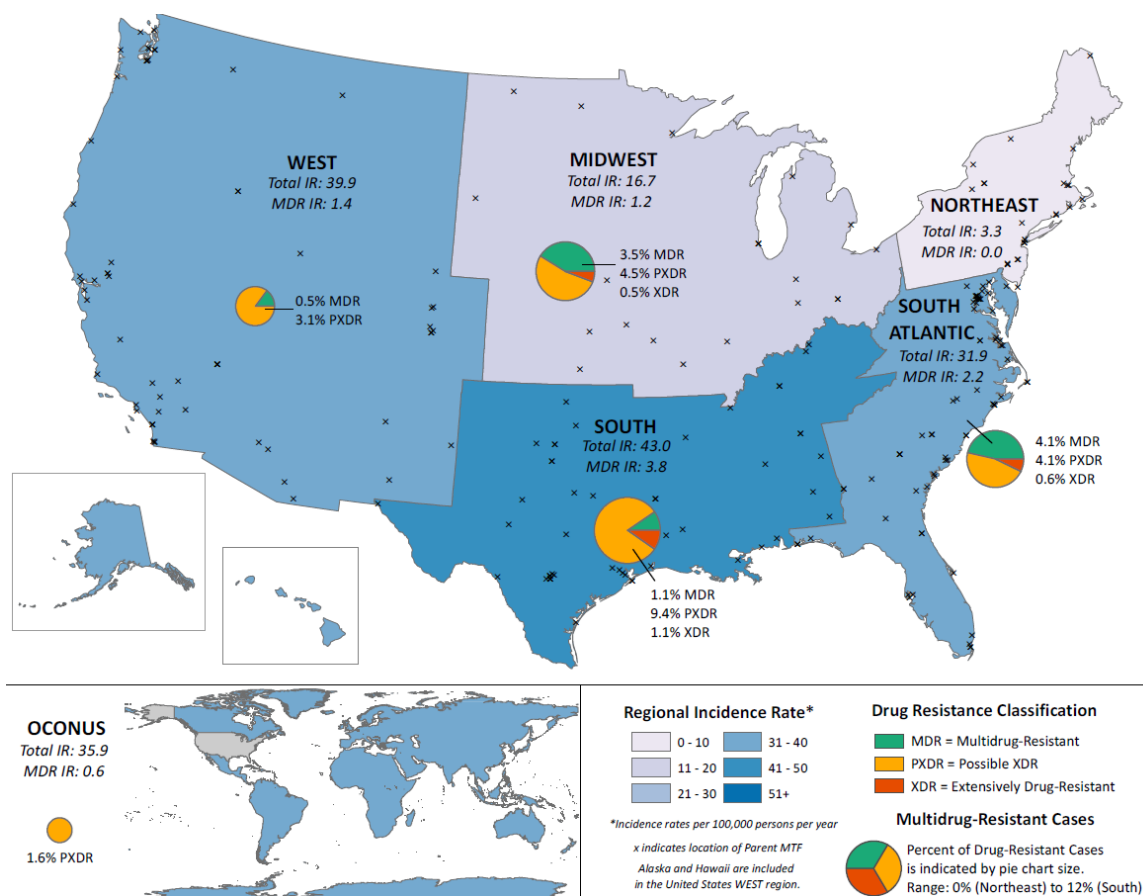


## Section B – Antimicrobial Resistance and Use

### Regional Multidrug Resistance

In 2015, the annual incidence rate was highest in the South (43.0 per 100,000 persons per year) and the West (39.9 per 100,000 persons per year) (Figure 4). The MDR *P. aeruginosa* incidence rate was highest in the South (3.8 per 100,000 persons per year) and the South Atlantic (2.2 per 100,000 persons per year). In all five regions with a MDR *P. aeruginosa* infection, the majority of infections were PXDR. The South, South Atlantic, and Midwest were the only regions to report confirmed XDR *P. aeruginosa* infections. There were no MDR *P. aeruginosa* infections in the Northeast.

**Figure 4.** Annual Incidence Rate (IR) and Percentage of Multidrug Resistance among *P. aeruginosa* Infections in the MHS by Region, CY 2015



Rates are presented as the rate per 100,000 persons per year.

Data Source: NMCPHC HL7-formatted CHCS microbiology, SIDR, and MHS M2 databases.
















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## Antibiogram

Table 6 displays an antibiogram for *P. aeruginosa* infections in the MHS from 2010-2015. Infections did not display 100% susceptibility to any of the relevant drugs tested. *P. aeruginosa* displayed significant increases in susceptibility to aztreonam and gentamicin and significant decreases in susceptibility to doripenem, imipenem, and ticarcillin/clavulanate. Despite *P. aeruginosa*'s decreasing susceptibility to doripenem, it had one of the highest overall trends of efficacy in 2015 at 95.2%, along with piperacillin at 95.2%. *P. aeruginosa* infections remained consistently susceptible to amikacin, cefepime, ceftazidime, meropenem, and tobramycin from 2010-2015 with susceptibility over 90.0%.

**Table 6.** Antibiogram of *P. aeruginosa* Infections Identified in the MHS, CY 2010-2015

Antibiotics	2010	2011	2012	2013	2014	2015	Susceptibility Trend	Comment <sup>a</sup>
Amikacin	95.3%	94.0%	95.1%	94.2%	94.8%	95.0%	100.0% 90.0% ] 	
Aztreonam	71.5%	77.1%	77.4%	78.4%	76.6%	79.4%	80.0% 70.0% ] 	↑
Cefepime	93.2%	92.3%	93.5%	93.5%	93.4%	92.7%	100.0% 90.0% ] 	
Ceftazidime	93.2%	95.1%	95.2%	94.7%	94.6%	94.8%	100.0% 90.0% ] 	
Ciprofloxacin	87.8%	87.1%	88.8%	86.8%	88.5%	87.5%	90.0% 80.0% ] 	
Colistin	91.8%	93.7%	98.8%	97.3%	95.1%	95.4%	100.0% 90.0% ] 	
Doripenem	100.0%	100.0%	100.0%	100.0%	97.5%	95.2%	100.0% 90.0% ] 	↓
Gentamicin	89.7%	87.0%	90.7%	90.5%	89.3%	91.3%	95.0% 85.0% ] 	↑
Imipenem	93.1%	92.4%	92.3%	90.2%	90.3%	90.6%	95.0% 85.0% ] 	↓
Levofloxacin	86.4%	84.4%	86.8%	84.9%	86.9%	84.8%	90.0% 80.0% ] 	
Meropenem	92.2%	93.8%	93.6%	94.2%	93.8%	92.2%	95.0% 85.0% ] 	
Piperacillin	94.7%	92.6%	96.1%	96.3%	93.5%	95.2%	100.0% 90.0% ] 	
Piperacillin/Tazobactam	93.9%	95.8%	94.2%	94.4%	93.6%	93.5%	100.0% 90.0% ] 	
Ticarcillin/Clavulanate	85.2%	85.6%	84.2%	50.0%	42.0%	63.1%	90.0% 40.0% ] 	↓
Tobramycin	95.0%	94.8%	96.4%	95.4%	95.3%	95.0%	100.0% 90.0% ] 	

<sup>a</sup> Arrow indicates the antibiotics with a significant change in direction of trend for significant two-tailed Cochrane-Armitage tests for trend established for a single antibiotic over time. A significant increase in susceptibility is denoted by a green upward arrow and a significant decrease in susceptibility is denoted by a blue downward arrow.

Data Source: NMCPHC HL7-formatted CHCS microbiology database.

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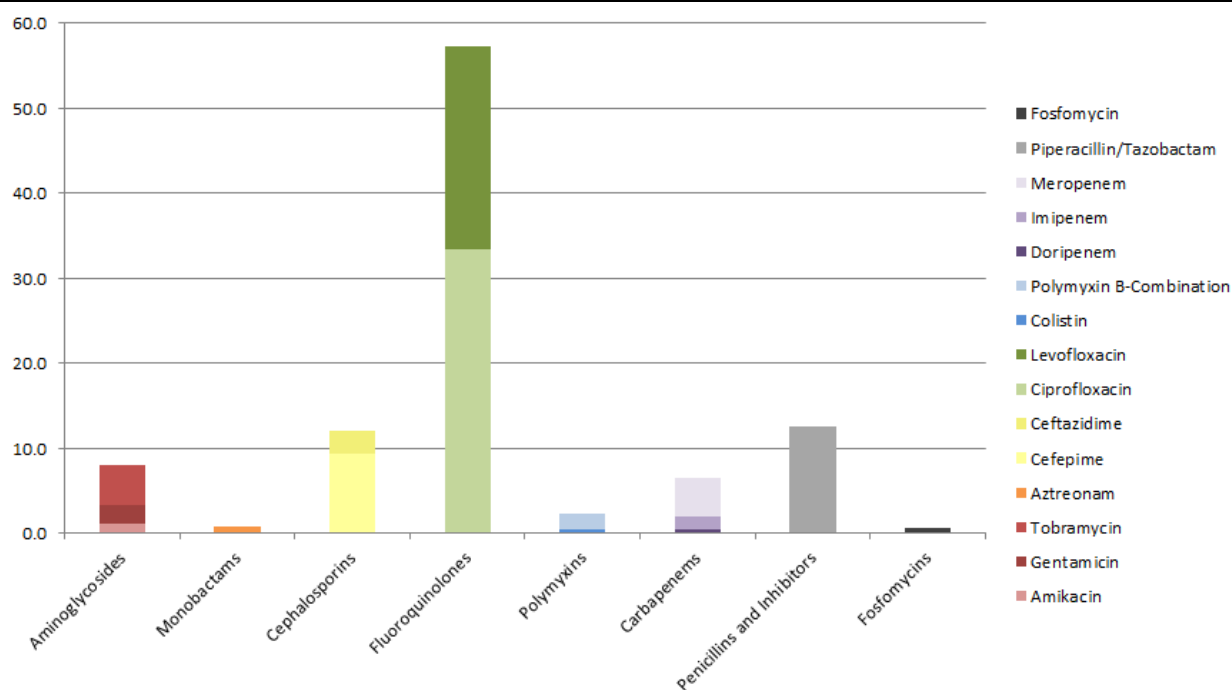




## Antimicrobial Consumption/Prescription Practices

In 2015, the most commonly prescribed antibiotics associated with *P. aeruginosa* infections were fluoroquinolones. Levofloxacin and ciprofloxacin comprised 57.3% of all prescribed antibiotics associated with *P. aeruginosa* infections in the MHS (Table 7). Penicillins and inhibitors (piperacillin/tazobactam) accounted for 12.6% of all prescriptions and cephalosporins (cefepime and ceftazidime) accounted for 12.0% of all prescriptions. Fosfomycin and polymyxins each accounted for less than 1.0% of all prescriptions associated with a *P. aeruginosa* infection.

**Table 7.** *P. aeruginosa* Infection and Prescription Practices in the MHS, CY 2015



Only the first occurrence of a unique antibiotic was counted per person per infection, regardless of administration route. Antibiotics measured in percentages.

Data Source: NMCPHC HL7-formatted CHCS microbiology and HL7-formatted pharmacy databases.

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## Section C – Special Populations

In 2015, there were 9 DON deployment-related *P. aeruginosa* infections among 3,587 prevalent infections in the MHS. Of these infections, 89.0% were male and 11.0% were female. Of the 9 infections, 11.2% were found in service members aged 18 to 24, 44.4% were found in those aged 25 to 34, and 44.4% were found in those aged 35 to 44.



## Discussion

The incidence of *P. aeruginosa* infection in the MHS increased in 2015 compared to the historical average. The incidence of *P. aeruginosa* shows an increasing trend over the last five years across all beneficiary populations. *P. aeruginosa* is an opportunistic infection, so it is unsurprising that it most affected the oldest and youngest populations. The incidence rate in individuals over the age of 65 was over 50.0% higher than the incidence rate identified for the entire MHS. This increase in incidence and an aging population allows for more opportunity for infection. As *P. aeruginosa* is commonly sourced from a previous health care exposure, continuing efforts to monitor transmission within the hospital setting is essential to stopping the increasing incidence trend. *P. aeruginosa*'s minimal nutritional requirements, as well as its tolerance to a wide range of physical conditions, have shown that environmental reservoirs contribute substantially to the spread of infection.

According to the CDC, *P. aeruginosa* is the fifth most common pathogen implicated in all hospital-acquired infections.<sup>10</sup> In the MHS, about 47.0% of all prevalent infections were identified as HA, which is consistent with previous year's findings, but surprising compared to the literature. There are a few possible reasons that the majority of infections in the MHS were identified as CA. First, a HA case is defined here by an inpatient admission. This definition does not take into consideration outpatient facilities, long-term care facilities, or clinics (such as dialysis centers) where a patient might also have an exposure. Second, *P. aeruginosa* is the most significant pathogen in cystic fibrosis (CF).<sup>21</sup> It infects 60.0% of all CF patients, with an 80.0% prevalence in CF patients less than 18 years of age.<sup>21</sup> It is believed that CF patients are infected from environmental sources, but it is possible to spread infection from CF patient to CF patient.<sup>21</sup> The CF population could not accurately be identified throughout the MHS for a sub-analysis, but they are a population that might have regular outpatient treatment as opposed to an inpatient admission. Such treatments would allow for healthcare-related exposures outside of hospitalization-related exposures.

The evaluation of exposure burden metrics found that the admission MDRO prevalence rate was close to the overall MDRO prevalence rate. This implies that of all MDRO infections that occurred at any time during an admission, most of them were identified within the first three days of admission and were thus CO cases as opposed to HO cases. These MDRO metrics align with findings from the HA analysis for all unique infections.

The rise of MDR *P. aeruginosa* is a growing concern both inside and outside of the hospital setting. Infections caused by resistant strains have been found to be associated with a three-fold higher mortality rate in the US. In the MHS in 2015, 7.6% of all prevalent *P. aeruginosa* infections were MDR, and most of these were classified as PXDR. *P. aeruginosa* infections in the MHS did not display 100.0% susceptibility to any drugs in 2015. Within 3 years, *P. aeruginosa* infections that were 100.0% susceptible to doripenem have dropped to 95.2% susceptible and are displaying a significant decreasing susceptibility trend. The most common prescribed antibiotics associated with a *P. aeruginosa* infection were ciprofloxacin and levofloxacin, but in 2015 they both had less than 90.0% efficacy in the MHS. Literature suggests that *P. aeruginosa* has been showing increasing resistance to both ciprofloxacin and



levofloxacin in the US, as well as to other antibiotics such as ticarcillin and aztreonam. With seriously ill immunocompromised hosts, combined therapy is a recommended treatment before susceptibility results are received.<sup>18</sup> Piperacillin and cephalosporins (cefepime and ceftazidime) showed efficacy greater than 90.0% in the MHS in 2015, and both were the next most frequently prescribed drugs associated with a *P. aeruginosa* infection. This suggests that in the MHS ciprofloxacin and levofloxacin are used as the first line of defense, but are likely followed by piperacillin and cephalosporins for infections that are resistant.

Due to the decreasing efficacy of relevant antibiotics, the rise of MDR *P. aeruginosa*, and the resilient nature of the organism, continued surveillance of *P. aeruginosa* is recommended. Further understanding of how *P. aeruginosa* affects the MHS population is needed to curb the rising incidence trend. Potential future analyses should focus on CF patients as a subpopulation and further comparing the types of infections defined as HA versus CA.



## Limitations

HL7-formatted data are generated within the CHCS at fixed MTFs; therefore, this analysis does not include microbiology records from purchased care providers, shipboard facilities, battalion aid stations, or in-theater facilities.

Microbiology data are useful for identifying laboratory-confirmed infections. However, infections that were treated presumptively without laboratory confirmation do not exist in the microbiology data. Clinical practice with regards to culturing varies between providers and facilities. Examples of situations where cultures may not be performed include confirmatory tests for patients with influenza-like illness (ILI) symptoms, or patients with superficial infections who are treated presumptively. Therefore, infection counts identified here may be an underestimate of the actual burden of *P. aeruginosa* in the MHS.

The data restructuring process for the analysis of clinical characteristics and antimicrobial resistance does not capture non-standard CHCS records. These non-standard records may include those containing the results of tests performed at reference laboratories or novel organism antibiotic combinations. The use of microbiology data for analysis of antibiotic resistance is also limited by the practice of cascade reporting, in which antibiotic sensitivity results are conditionally reported in CHCS to guide antimicrobial selection and treatment decisions. Cascade reporting is practiced to varying degrees at MHS MTFs.

The EDC data feed does not include records on medical encounters conducted outside the MHS (e.g., purchased care in the community) and it cannot be determined if an individual truly had no healthcare contact or other risk factors for *P. aeruginosa* infection, or if the individual had a risk factor that was not visible in the available data. Data on other factors commonly used to define HA cases were not available (e.g., presence of an invasive device, history of dialysis or surgery, a long-term care facility stay in the 12 months preceding the culture). Therefore, there may be HA cases currently miscategorized as CA cases. Without the ability to identify these HA cases, a more accurate estimate of CA cases could not be determined. Given the relatively healthy military population, however, any misclassification bias is likely minimal.

The pharmacy databases consist of outpatient non-intravenous prescriptions (outpatient), inpatient non-intravenous prescriptions (unit dose), and intravenous prescriptions (intravenous). Though treatment compliance in the inpatient setting can be assumed, outpatient pharmacy records indicate that a patient received a prescription and subsequent compliance is unknown. Due to near real-time data feeds, analysts are able to determine if a prescription was edited or canceled; however, the time difference between these events may allow for a short period of treatment not considered in this analysis. During ongoing surveillance efforts, patient treatment status may change as edited or canceled prescription records are received.

It is possible that not all antibiotic prescriptions were dispensed in response to a *P. aeruginosa* infection. Antibiotics that were prescribed within the appropriate timeframe to be associated with a *P. aeruginosa* specimen collection date may have actually been provided for reasons other than the documented infection, such as a different infection occurring after *P. aeruginosa* was



identified. However, most antibiotics identified as being associated with a *P. aeruginosa* infection were antibiotics that are typically used to treat *P. aeruginosa*, so it is likely that the majority of prescriptions in this analysis were truly in response to the *P. aeruginosa* infection.

DMDC provides monthly snapshots of each active duty, reserve, and deployed Navy and Marine Corps service member's personnel record. Data are provided to DMDC by the service and analyses are dependent on the quality and completeness of these data. Any changes in service member status after the monthly data are extracted will not be captured until the following month. Active duty and reserve personnel records are maintained in separate databases, but activated reservists may be captured in the active duty DMDC file rather than the reserve DMDC file. Unit Identification Codes (UICs) reported for Marine Corps service members represent Reporting Unit Codes (RUCs), rather than UICs.

Personnel records for deployed service members are provided via CTS. The purpose of DMDC CTS is to capture personnel information for Central Command (CENTCOM) deployments. Additionally, deployment start and end dates are derived from the following systems and may not reflect the actual dates of deployment: Defense Finance Accounting System (DFAS), the Deployed Theater Accountability System (DTAS), the Secure Personnel Accountability System (SPA), historical PERSTEMPO files, and the Individual Personnel TEMPO Program. A country location of ZZ may represent shipboard or an unknown deployment location.

Infections may not be uniformly distributed within a spatial region; no distinctions were made with regard to the heterogeneity of incidence rates or prevalence among subunits (e.g., states, non-US countries). The choropleth maps represent an annual snapshot of infections and do not reflect the geographic movement of service members within the course of a year. Infections were georeferenced according to the locations of the MTFs where they were encountered, not according to the deployment locations or home locations of the service members. Map area does not equate to population size; parent MTF locations are displayed within US regions to convey the density of military medical facilities within each region.

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## Appendix A: Antibiotics Included in Resistance Definitions

**Table A1:** Antibiotics Included in the Resistance Definitions for *P. aeruginosa* Infections in the DOD, CY 2015

Antibiotic Class	Antibiotics Included in Class
Aminoglycosides	Gentamicin
	Tobramycin
	Amikacin
	Netilmicin
Carbapenems	Imipenem
	Meropenem
	Doripenem
Cephalosporins	Ceftazidime
	Cefepime
Fluoroquinolones	Ciprofloxacin
	Levofloxacin
Penicillins + $\beta$ -lactamase inhibitors	Ticarcillin-clavulanic acid
	Piperacillin-tazobactam
Monobactams	Aztreonam
Phosponic acids	Fosfomycin
Polymyxins	Colistin
	Polymyxin B

Source: Magiorakos et al., 2012.

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## Appendix B: Acronym and Abbreviation List

Acronym/Abbreviation	Definition
AD	active duty
BSI	bloodstream infection
CA	community-associated
CDC	Centers for Disease Control and Prevention
CENTCOM	Central Command
CF	cystic fibrosis
CHCS	Composite Health Care System
CLSI	Clinical and Laboratory Standards Institute
CO	community-onset
CONUS	continental United States
CTS	Contingency Tracking System
CY	calendar year
DFAS	Defense Finance Accounting System
DMDC	Defense Manpower Data Center
DOD	Department of Defense
DON	Department of the Navy
DTAS	Deployed Theater Accountability System
EDC	EpiData Center Department
HA	healthcare-associated
HAI	healthcare-associated infection
HL7	Health Level 7 format
HO	hospital-onset
ICD-9-CM	International Classification of Diseases, Ninth Revision, Clinical Modification
ICD-10-CM	International Classification of Diseases, Tenth Revision, Clinical Modification
ILI	influenza-like illness
IR	incidence rate
IV	intravenous
M2	Military Health System (MHS) Management Analysis and Reporting Tool
MDR	multidrug-resistant
MDRO	multidrug-resistant organism
MEPRS	Medical Expense and Performance Reporting System
MHS	Military Health System
MTF	military treatment facility
NHSN	National Healthcare Safety Network
NMCPHC	Navy and Marine Corps Public Health Center
OCONUS	outside the continental United States
OP	outpatient
PDR	pandrug-resistant
PPDR	possibly pandrug-resistant
PXDR	possibly extensively drug resistant
RUC	Reporting Unit Codes
SHEA	Society for Healthcare Epidemiology of America
SIDR	Standard Inpatient Data Record



Acronym/Abbreviation	Definition
SPA	Secure Personnel Accountability system
SSTI	skin and soft tissue infection
UIC	Unit Identification Codes
UD	unit dose
US	United States
UTI	urinary tract infection
XDR	extensively drug-resistant

